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Delay aversion in attention deficit/hyperactivity disorder is mediated by amygdala and prefrontal cortex hyper-activation

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Background: Experimental research supports delay aversion as a motivational feature of attention deficit/hyperactivity disorder (ADHD). To investigate the neurobiology of delay aversion in ADHD, this study examined whether adolescents with ADHD display an unusually strong activation in affective brain regions in response to cues predicting forthcoming delay and whether these effects are (a) delay-dose dependent and (b) statistically mediate the association between ADHD and self-reported delay aversion. **Methods:** Twenty-nine right-handed male adolescents with combined type ADHD and 32 typically developing controls (ages 10–18 years) performed a reaction time task in an MRI scanner. Pretarget cues indicated delay-related response consequences. One indicated that delay would follow the response irrespective of response speed (CERTAIN DELAY), a second that delay would only follow if the response was too slow (CONDITIONAL DELAY), and a third that no delay would follow the response whatever its speed (NO DELAY). Delay levels were 2, 6, or 14 s. Participants also rated their own delay aversion in everyday life. **Results:** Individuals with ADHD rated themselves as more delay averse than controls. Significantly greater activation to CERTAIN DELAY cues relative to NO DELAY cues was found in participants with ADHD compared to controls (bilaterally) in amygdala, anterior insula, temporal pole, dorsolateral prefrontal cortex (DLPFC), and ventromedial prefrontal cortex. Amygdala and DLPFC activation strength were strongly and delay-dose dependently correlated with delay aversion ratings, and statistically mediated the relationship between ADHD status and delay aversion. **Conclusions:** When presented with cues predicting impending delay, adolescents with ADHD, relative to controls, displayed a delay-related increase in activation in amygdala and DLPFC, regions known to be implicated in the processing of aversive events. Future studies should examine the specificity of these effects to delay aversion compared to aversive events in general. **Keywords:** Attention deficit/hyperactivity disorder; fMRI; delay aversion; amygdala; dorsolateral prefrontal cortex; affective network.

Introduction

Attention deficit/hyperactivity disorder (ADHD) implicates multiple brain systems (Sonuga-Barke, Cortese, Fairchild, & Stringaris, 2016). Emotional and cognitive impairments in ADHD are related to both structural (Hoogman et al., 2017; Norman et al., 2016) and functional (Bush, Valera, & Seidman, 2005; Norman et al., 2016; Paloyelis, Mehta, Kuntsi, & Asherson, 2007) brain abnormalities. Findings support a role for atypical brain regions known to mediate the processing of motivationally and emotionally salient stimuli and events (Knutson & Greer, 2008), manifest at a behavioral level as alterations in response to reinforcement (Plichta & Scheres, 2014). One of the most consistent findings in this regard is that individuals with ADHD are unusually sensitive to the imposition of a delay prior to reinforcement (Plichta et al., 2009). This produces

a characteristic preference for small immediate over larger delayed rewards, termed impulsive choice (Marco et al., 2009). One theoretical account postulates that impulsive choice in ADHD is the result of a two-component developmental process (Sonuga-Barke, 2005): First, early established fundamental alterations in brain reward circuits create a primary drive for immediate reward, linked to hypo-activation in the ventral striatum and related frontal regions in response to reward cues. This impairs an individual's ability to wait for future rewards. Second, over time, this primary drive for immediate reward promotes the acquisition of delay aversion – where negative affective states are increasingly elicited by delay-rich situations and settings where waiting is required. At a behavioral level this in turn motivates delay-averse individuals to avoid such settings – compounding the original primary preference for immediate rewards in choice settings and provoking increases in inattention and hyperactivity in nonchoice settings. There is broad support for delay aversion in ADHD from behavioral studies. For instance, Marco et al. (2009) found that linking the choice for a small immediate reward to a reduction in

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overall delay increased impulsive choice. Furthermore, ADHD is associated with elevated frustration following the imposition of an unexpected delay during task performance (Bitsakou, Antrop, Wiersma, & Sonuga-Barke, 2006), premature disengagement (Scime & Norvilitis, 2006), and higher levels of activity and inattention during long and boring tasks (Sonuga-Barke, Saxton, & Hall, 1998). In addition, individuals with ADHD show an attentional bias to delay cues, equivalent to the attentional bias to social threat cues seen in anxious individuals (Sonuga-Barke, De Houwer, De Ruiter, Ajzenstzen, & Holland, 2004).

Neurobiological predictions of the delay aversion hypothesis that delay aversion will be mediated by altered functioning of brain regions known to be involved, more generally, in the anticipation and response to aversive outcomes (especially the amygdala and related regions), were set out more than a decade ago (Sonuga-Barke, 2005). Initial support comes from two small-scale functional Magnetic Resonance Imaging (fMRI) studies (Lemiere et al., 2012; Wilbertz et al., 2013) that showed elevated levels of activity within these regions to cues predicting upcoming inescapable delay. Lemiere et al. (2012) compared adolescents with ADHD to age-matched typically developing controls on an adaptation of the Monetary Incentive Delay (MID) task (Knutson, Westdorp, Kaiser, & Hommer, 2000), where symbols presented on a screen indicated whether delay would be imposed after a slow response on a simple reaction time task. They found that ADHD was associated with increased amygdala and insula activation to cues signaling inescapable compared to escapable delay (Lemiere et al., 2012). Using a similar task, Wilbertz et al. (2013) compared brain responses to cues signaling delays of different lengths in adults with ADHD and controls. Here also, ADHD was associated with amygdala and insula hyper-activation to cues of impending delay (Wilbertz et al., 2013). The amygdala has been shown to frequently co-activate with the insula during processing of negative emotional stimuli (Hayes & Northoff, 2011; Lindquist, Wager, Kober, Bliss-Moreau, & Barrett, 2012). Consistent with their shared role in affective appraisal, particularly of negative stimuli (Stein et al., 2007), these two brain regions are highly connected anatomically and functionally (Mutschler et al., 2009).

To provide a more definitive examination of the functional neuroanatomy of delay aversion in ADHD, we tested the link between ADHD, delay aversion and brain activity using a task that combines the strengths of those used in the Lemiere et al. (2012) and Wilbertz et al. (2013) studies. We conducted whole-brain analyses of neural activation to cues signaling three different delay-related outcomes: One cue signaled that delay was inevitable irrespective of performance, one cue signaled that delay would not occur, and one cue signaled that a delay

would occur only if responding was too slow. We predicted that in adolescents with ADHD, relative to controls, cues predicting inevitable delay would elicit stronger activation within amygdala and related affective brain regions than cues predicting no delay or delay conditional on performance. We moreover predicted that these effects would be delay-dose dependent and that they would statistically mediate the relationship between ADHD and self-reported every day delay aversion.

Methods

The experimental protocol was approved by the ethics committee of the University Hospital Leuven, Leuven, Belgium (S54971). Prior to testing, participants and parents provided written informed consent.

Participants

Thirty-two right-handed male adolescents with combined type ADHD and 36 typically developing controls between the age of 10 and 18 years entered the study. Individuals with ADHD were recruited through the Child and Adolescent Psychiatry department of UPC - KU Leuven. All had a pre-existing clinical diagnosis of ADHD based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV), as assessed by a child psychiatrist. Presence, pervasiveness and clinical impact of ADHD symptoms across different settings (home and school) were confirmed using the parent Schedule for Affective Disorders and Schizophrenia for school-age children (K-SADS) (Kaufman et al., 1997) (Table 1). All ADHD participants met the clinical cut-off score on the Achenbach questionnaires for teachers (Teacher Report Form) and parents (Child Behavior Checklist) (Achenbach & Rescorla, 2001) and on the Disruptive Behavior Rating Scale (Pelham, Gnagy, Greenslade, & Milich, 1992; Dutch translation Oosterlaan et al., 2008). The control group was recruited from youth organizations and schools. Controls were excluded if they met DSM-IV criteria for any psychiatric disorder assessed using a K-SADS screening interview with one of the parents. All subjects completed the Dutch adaptation of the Wechsler Intelligence Scale version 3 for Children (short version; Kort et al., 2005) or Adults (Wechsler, 2005), using the vocabulary, similarities, block design and picture arrangement subtests (Sattler, 2001). Participants were excluded if parents reported specific learning disorders (e.g. dyslexia or dyscalculia), drug or substance abuse, neurological abnormalities, or MRI contraindications. Twenty-four of the individuals with ADHD were taking psychostimulant medication. Medication was withheld for 72 hr prior to testing and fMRI scanning. Table 1 reports participant characteristics.

Task design

During fMRI signal acquisition, participants completed a reaction time task based on the MID task (Broyd et al., 2012; Knutson et al., 2000; Lemiere et al., 2012). Each trial had five phases: (a) delay cue (250 ms in duration), (b) variable anticipation period (containing a 3–3.5 s fixation cross), (c) target stimulus (1.45 s), (d) outcome (3 s), and (e) delay period (0, 2, 6, or 14 s) (Figure 1). Participants were instructed to press a button as quickly as possible upon presentation of the target stimulus. The delay cue indicated the delay consequence that would follow after responding to the target. There were three conditions differentiated by delay cue type: (a) in CERTAIN DELAY trials (signaled by a triangle-shaped cue) a postresponse delay period was imposed irrespective of the speed of the

Table 1 Group characteristics

Characteristic	ADHD (<i>n</i> = 29)		Control (<i>n</i> = 32)		<i>p</i> -value independent <i>t</i> -test
	Mean	<i>SD</i>	Mean	<i>SD</i>	
Age (in years)	14.51	2.14	14.74	2.10	.68
Full scale intelligence quotient	99.53	9.56	111.64	10.20	<.001
Verbal quotient ^a	97.34	13.45	109.53	10.78	<.001
Performance quotient ^b	101.06	10.58	112.78	12.65	<.001
Total Quick Delay Questionnaire score ^c	25.38	7.57	9.02	5.92	<.001
Delay aversion subscale	14.52	5.76	4.62	3.58	<.001
Task performance (in ms)					
CERTAIN DELAY	294.25	50.69	277.64	35.51	.13
CONDITIONAL DELAY	269.03	31.00	287.43	47.10	.06
NO DELAY	284.74	45.45	270.40	33.26	.13
Comorbidity ^d	Oppositional defiant disorder (<i>n</i> = 3)				

^aEstimated on basis of vocabulary and similarities subtests.

^bEstimated on basis of block design and picture arrangement subtests.

^cBased on the self-report version of the Quick Delay Questionnaire.

^dBased on the Schedule for Affective Disorders and Schizophrenia for school-age children.

response to the target; (b) in CONDITIONAL DELAY trials (signaled by a circle-shaped cue), delay was imposed only if participants responded too slowly (delay frequency was set at one-third of the trials); and (c) in NO DELAY trials (signaled by a diamond-shaped cue) there was no delay regardless of response speed (Figure 1). Three levels of delay were used (2, 6, and 14 s), indicated by the presence of one, two, or three horizontal lines within the delay cue, respectively. The delay durations were selected based on prior studies and on the need to take account of the exponential nature of time perception (Lemiere et al., 2012; Wilbertz et al., 2013). The length of the anticipation period that followed the delay cue was jittered so that target presentation remained unpredictable. Unbeknown to participants, the threshold for response speed was adapted individually, so that participants would succeed in two-thirds of trials across all three cue conditions. At the start of fMRI acquisition, the reaction time (RT) window was derived based on 27 practice trials prior to scanning. The RT was continually adapted throughout the task, based on a staircase tracking algorithm (20ms increase/decrease). Participants received feedback about their performance – a green ‘OK’ sign (fast enough) or a red cross (too slow). During delay periods the length of the delay was visualized with a white bar. Participants were presented with a total of 189 trials – 63 of each type. Trials were presented in a pseudorandom order in seven blocks of 27 trials. Participants were told that the task would last for 30–45 min subdivided into seven games and that task duration was contingent upon performance. In reality, performance did not affect task duration. Each run lasted 5.5 min and total task duration was 38.5 min. Participants received €50 upon study completion.

Subjective ratings of delay aversion in everyday life

Participants completed the self-report Quick Delay Questionnaire (QDQ), which includes a five-item delay aversion subscale: (a) I am usually calm when I have to wait in queues, (b) I feel relaxed when waiting for things, (c) I hate waiting for things, (d) I feel frustrated when I have to wait for someone else to be ready before I can do something, and (e) having to wait for things makes me feel stressed and tense. The delay aversion QDQ subscale had good internal and test-retest reliability in a sample of older teenage/young adult students (Clare, Helps, & Sonuga-Barke, 2010) and adequate internal reliability in a sample of children with and without ADHD (Hsu, Benikos, & Sonuga-Barke, 2015). Internal reliability of the subscale in the current sample was high (Cronbach’s $\alpha = .82$).

fMRI acquisition

Before scanning, participants were familiarized with the scanner and received additional oral instructions on task procedures. Practice trials were performed, accompanied by a description of the task. Cue valence ratings confirmed that all participants had learned the association between delay cue symbols and the nature of the upcoming delay. MR images were acquired at the radiology department, University Hospital Leuven, Belgium, on an Intera[®] 3T MR scanner (Philips Medical Systems, Best, The Netherlands) using an 8-channel SENSE head coil. Whole brain Blood Oxygen Level Dependent (BOLD) axial Echo Planar Images were obtained using fixed scan parameters: TR = 2,000 ms, TE = 30 ms, 90° flip angle, 220 × 220 mm² field of view, 80 × 80 matrix, without a slice gap, SENSE reduction factor = 2, 36 sequential bottom-up slices with a slice thickness of 3.5 mm and in plane voxel size of 2.75 mm². In the middle of each scanning session, a high-resolution structural scan was acquired using a T1-weighted gradient to facilitate localization and co-registration of functional data. Structural scan parameters were: TR = 9.7 ms, TE = 4.6 ms, inversion time = 1,100 ms, 12° flip angle, 256 × 256 mm² field of view, 256 × 256 matrix and 1 mm³ voxel size. Stimuli were displayed using Presentation software (version 14.6, Neurobehavioral Systems, Berkeley, CA). Head movement was minimized using a headphone with additional foam fittings.

Image preprocessing

Prior to statistical analysis, standard preprocessing was performed in Statistical Parametric Mapping 8 (SPM 8) (Wellcome Department of Neuroimaging, London, UK, <http://www.fil.ion.ucl.ac.uk/spm>). Data preprocessing included manual reorienting of both structural and functional images to the anterior and posterior commissure line, slice time correction of functional images, realignment of functional images using the middle slice of each run as a reference, co-registration of the structural image to the mean functional image, segmentation of the structural image based on specific adolescent tissue probability maps in Montreal Neurological Institute (MNI) space created with the Template-O-Matic toolbox (Wilke, Holland, Altaye, & Gaser, 2008), spatial normalization of all images, and smoothing of functional images using a 3D Gaussian kernel of 8 mm FWHM. After realignment, motion correction parameters were inspected and subjects with more than 2 mm translation and 2° rotation were excluded (four controls and three ADHD patients).

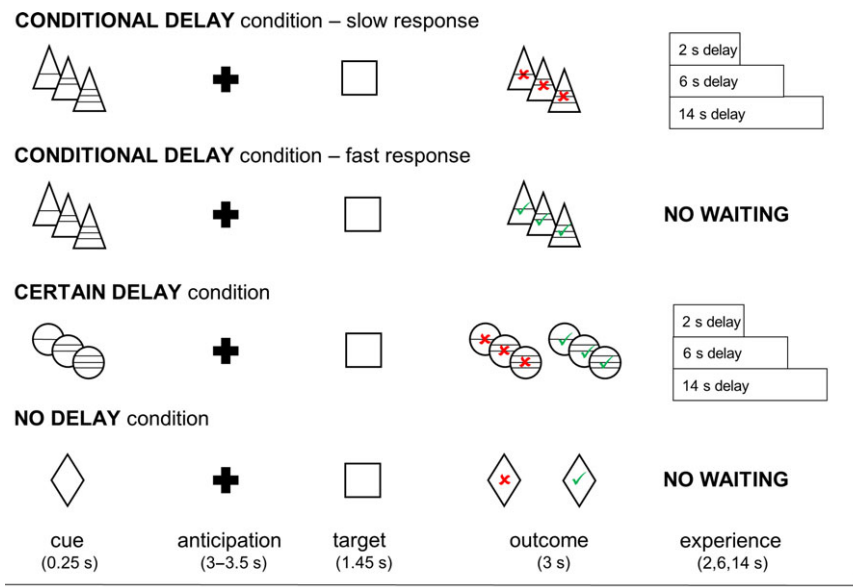


Figure 1 Task design. Delay cues indicated different delay-related response consequences. The triangle (CONDITIONAL DELAY) indicated that delay would only follow after slow responses (on 33% of trials). The circle (CERTAIN DELAY) indicated that delay would follow irrespective of response speed. The diamond indicated that no delay would follow, irrespective of response speed (NO DELAY). Delay levels were 2, 6, or 14 s and were indicated by one to three horizontal bars inside the cue. The analysis focused on delay anticipation

Statistical analysis

Task performance. Repeated-measures ANOVAs examined the effects of condition (CERTAIN DELAY, CONDITIONAL DELAY, NO DELAY) as a within-subject factor and group (ADHD, CONTROL) as a between-subject factor on reaction time (RT). To examine the effect of delay level, further ANOVAs were conducted with delay length (2, 6, 14 s) and task condition (CERTAIN DELAY, CONDITIONAL DELAY) as within-subject factors and group as a between-subject factor. Post-hoc *t*-tests were used to explore significant interaction effects ($p < .05$).

Cue-elicited brain activation. For each subject, using SPM 8, a general linear model was estimated using eight regressors of interest: three cue conditions (CERTAIN DELAY, CONDITIONAL DELAY, NO DELAY), two possible outcomes (fast enough or too slow response) and three possible delay periods (2, 6, and 14 s), and seven regressors of no interest: one for the time period of outcome and delay presentation and six motion parameters. Two main T-contrast images CERTAIN DELAY > NO DELAY and CONDITIONAL DELAY > NO DELAY were calculated for each subject. In addition, to examine the delay dose-response curve three additional first-level T-contrast images were created: CERTAIN DELAY 2 s > NO DELAY, CERTAIN DELAY 6 s > NO DELAY, CERTAIN DELAY 14 s > NO DELAY.

Individual contrast images were used in a second-level analysis in a three-stage process. First, whole-brain analyses were performed on the main contrasts (CERTAIN DELAY > NO DELAY and CONDITIONAL DELAY > NO DELAY). Whole-brain family wise error (FWE) corrected ($p < .05$) significant voxels and clusters were identified based on the peak beta-value and labelled using the SPM12 atlas provided by neuromorphometrics. Second, the effect of delay dose was examined for regions showing FWE-corrected ($p < .05$) significant responses to delay cues in the whole-brain analysis (CERTAIN DELAY > NO DELAY). For this purpose, contrast estimates were extracted for the individual delay contrasts at the coordinates of significantly activated group peak voxels. Repeated-measures ANOVA using delay length (2, 6, 14 s) as within- and group

as between-subject factors with subsequent contrasts were used to explore delay effects within each group separately. The following bilateral ROIs were defined: ventromedial prefrontal cortex (VMPFC), dorsolateral prefrontal cortex (DLPFC), anterior insula, amygdala and temporal pole. Significance was determined at $p < .01$ to approximate Bonferroni-corrected $p < .05$ for the five ROIs. Individual brain activations with a deviance of more than two standard deviations from the mean group activation were excluded from the analysis - seven individual brain activations were removed (1 amygdala 6 s, 2 temporal pole 2 s, 1 VMPFC 2 s, 1 VMPFC 6 s and 2 VMPFC 14 s). Finally, for those regions showing a significant delay dose-response relationship in the ADHD group, a mediational analysis was performed. First, groups were compared on QDQ delay aversion scores using independent *t*-tests. Second, an index of the contrast between CERTAIN DELAY and NO DELAY cue activation was calculated and multiple regression analysis was conducted to test whether this index mediated the relationship between ADHD group membership and QDQ delay aversion scores using a bootstrapping method, in which the indirect effect was evaluated after 5,000 bootstrap resamples using a 95% confidence interval (Preacher & Hayes, 2008). Percent mediation and standardized indirect effect confidence intervals were used to indicate the mediation effect size (Preacher & Kelley, 2011).

Results

Task performance

RTs were shorter on CONDITIONAL DELAY and NO DELAY trials than on CERTAIN DELAY trials ($F = 12.60$; $p < .001$, $\eta_p^2 = .16$; Table 1). RT standard deviation was in general higher in the ADHD group ($p = .04$). There was no interaction between cue type and group for RT ($F = 0.68$; $p = .55$, $\eta_p^2 = .009$). No main effect of delay length was found ($F = 0.85$; $p = .43$, $\eta_p^2 = .013$).

fMRI data

Whole-brain analyses. Tables S1 and S2 report whole-brain activation as a function of cue type and group. Relative to controls, in ADHD participants there was significantly greater activation averaged over both hemispheres in the temporal pole ($t = 4.53$; p [FWE] $< .001$), the amygdala ($t = 3.60$; p [FWE] $< .01$), the anterior insula ($t = 3.54$; p [FWE] $< .05$), the ventromedial prefrontal cortex (VMPFC) ($t = 4.05$; p [FWE] $< .01$), and the dorsolateral prefrontal cortex (DLPFC) ($t = 3.91$; p [FWE] $< .01$) for the CERTAIN DELAY > NO DELAY contrast (Figures 2 and 3). For the CONDITIONAL DELAY > NO DELAY contrast, similar but smaller differences between ADHD and control participants were seen that did not survive FWE-correction (Figure 2). Subsequent dose-response analyses therefore only focused on the CERTAIN DELAY > NO DELAY contrast.

The effect of delay length

There was a significant group \times dose interaction for amygdala activations ($F = 3.57$; $p = .01$; $\eta_p^2 = .06$), with increasing activations as a function of delay in the ADHD but not the control group (Figure 4). Post-hoc tests showed significant differences between delay levels for the ADHD group (2–6 s, $t = 2.78$; 6–14 s, $t = 3.30$; 2–14 s, $t = 4.93$). For DLPFC activations, the differential effect of delay length was not significant overall ($F = 1.25$; $p = .29$; $\eta_p^2 = .02$). However, when analysis was restricted to the 2 s and 14 s delays, a significant interaction was observed ($F = 4.72$; $p < .05$; $\eta_p^2 = .14$), with stronger activations to 14 s than 2 s cues in the ADHD group but not the control group ($t = 2.63$). No effect of delay length was seen for temporal pole, anterior insula, or VMPFC ($p > .05$) (Figure 4).

Mediational analysis

On the basis of the effects of delay length reported above, both amygdala and DLPFC activation were included in the mediational analysis to examine whether the difference in brain activation to CERTAIN DELAY and NO DELAY cues mediates the relationship between ADHD status and self-reported delay aversion. Individuals with ADHD rated themselves as significantly more delay averse than controls on the QDQ delay aversion scale (Table 1). Across both groups, these QDQ delay aversion scores were significantly associated with the index of the contrast between CERTAIN DELAY and NO DELAY cue activations in the amygdala for 14 s delay cues ($r = .55$; $p < .001$), in the DLPFC for 6 s delay cues ($r = .27$; $p = .02$) and in the DLPFC for 14 s delay cues ($r = .47$; $p < .001$) (Figure 5A; Figure S1). The QDQ score was also significantly correlated with delay-related neural activity in the

ADHD (amygdala 14 s = 0.39, $p < .05$; DLPFC 14 s = 0.38, $p < .05$) and control (amygdala 14 s = 0.43, $p < .01$; DLPFC 14 s = 0.46, $p < .01$) groups separately. The degree of association was larger on trials with longer delays (Figure 5A; Figure S1). Therefore, the mediational analyses focused on 14 s delay cues (effects were similar if analyses were collapsed across all delay levels). Multiple regression analyses were performed to assess each component of the proposed mediation model (Figure 5B). First, it was found that group was positively associated with QDQ delay aversion ratings ($\beta = .67$, $t = 7.03$, $p < .001$). Second, group was positively associated with CERTAIN DELAY and NO DELAY cue-related differences in amygdala activation ($\beta = .43$, $t = 3.68$, $p < .001$) and DLPFC activation ($\beta = .35$, $t = 2.88$, $p < .001$) in response to 14 s delay cues. Third, QDQ delay aversion ratings were positively associated with cue-related differences in amygdala ($\beta = .55$, $t = 4.56$, $p < .001$) and DLPFC ($\beta = .47$, $t = 3.92$, $p < .001$) activation. Finally, the group difference in QDQ delay aversion ratings was significantly mediated by amygdala ($\beta = .53$, $t = 5.45$, $p < .001$) and DLPFC ($\beta = .58$, $t = 5.99$, $p < .001$) activation differences. The standardized indirect effect for amygdala (95% CI: 0.19–0.30) and DLPFC (95% CI: 0.12–0.21) activation indicated small to medium effect sizes. The indirect effect accounted for 18% (amygdala) and 24% (DLPFC) of the interaction between group and delay aversion score.

Discussion

The delay aversion hypothesis of ADHD is based on the idea that symptoms of impulsiveness, inattention and hyperactivity are, in part, determined by a motivation to escape or avoid the excessive negative affect that individuals with ADHD experience when they are confronted with a delay prior to the delivery of a reward or the completion of a task (Sonuga-Barke, 1994). There is empirical evidence that individuals with ADHD do indeed find delay aversive (Clare et al., 2010; Hsu et al., 2015). Our current data from the QDQ provide further support for this notion, in that adolescents with ADHD rate themselves as more delay averse than age-matched controls. At a neurobiological level, this delay-related negative affect should manifest as hyper-activation within those brain regions of the limbic system known to be implicated more generally in the processing of aversive experiences – particularly amygdala and insula (Hayes & Northoff, 2011; Lindquist et al., 2012). The results of two earlier small-scale fMRI studies have provided preliminary evidence to support this prediction of the theory (Lemiere et al., 2012; Wilbertz et al., 2013). The current results, from a much larger sample, confirm and extend these findings in a number of important ways. First, as a group, individuals with ADHD compared to controls displayed an enhanced, dose-

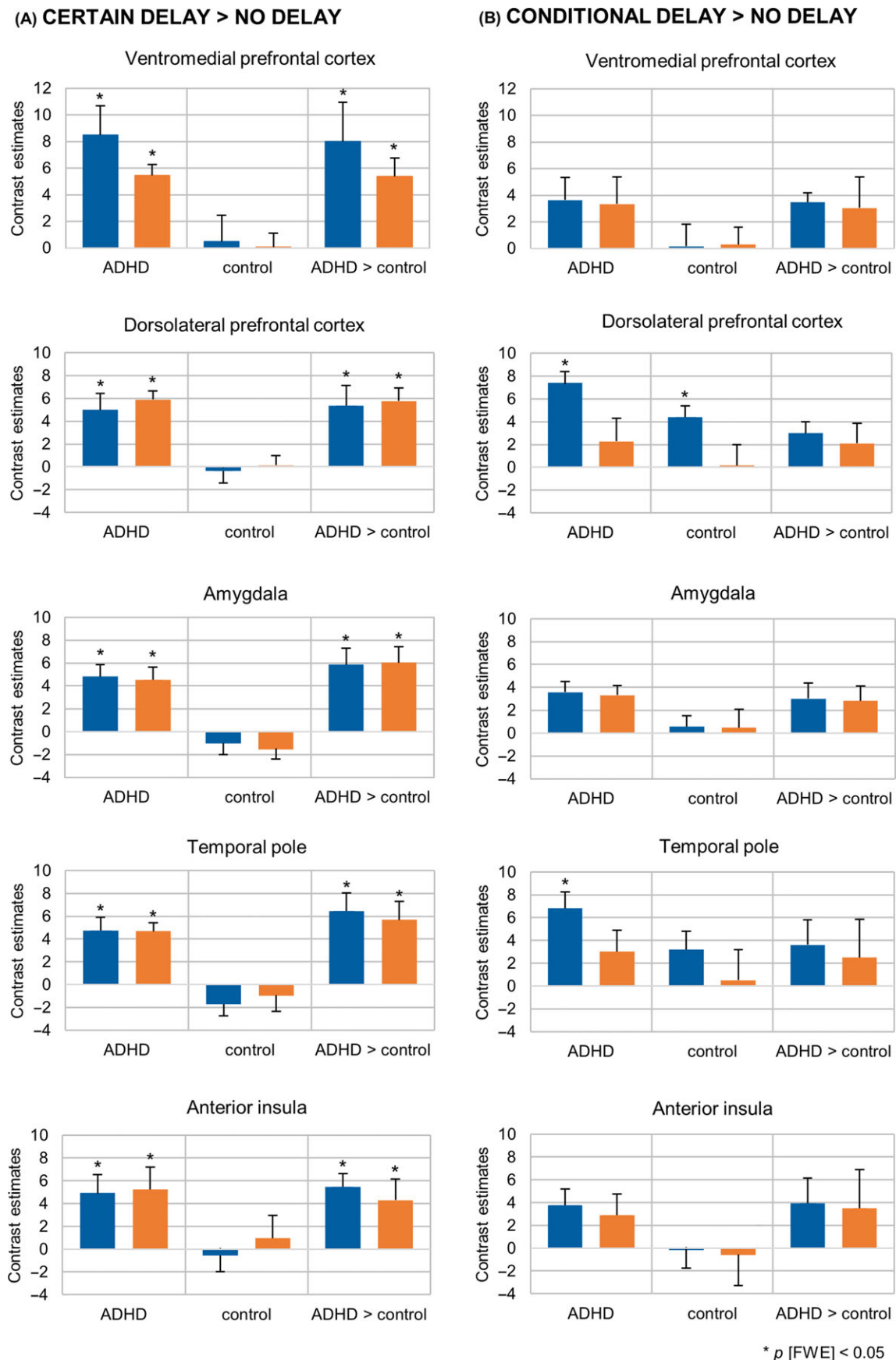


Figure 2 Extracted contrast estimates at peak activation clusters for (A) CERTAIN DELAY > NO DELAY and (B) CONDITIONAL DELAY > NO DELAY contrasts in the left (blue) and right (orange) ventromedial prefrontal cortex, dorsolateral prefrontal cortex, amygdala, temporal pole and anterior insula for ADHD, control and group contrast. Error bars display the standard error. Asterisks (*) indicate $p [FWE] < .05$

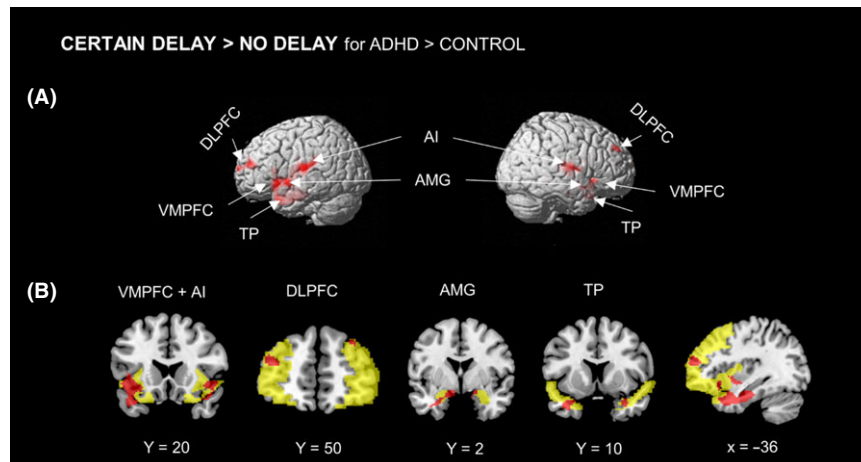


Figure 3 (A) Increased activation in the ADHD group compared to the control group was found during anticipation of CERTAIN DELAY > NO DELAY in the ventromedial prefrontal cortex (VMPFC), dorsolateral prefrontal cortex (DLPFC), amygdala (AMG), temporal pole (TP) and anterior insula (AI). (B) The same activations as in A (red), but displayed on cross-sectional coronal slices and one sagittal slice. The anatomical boundaries of these regions are shown in yellow. For visualization purposes, cluster activation is displayed at $p < .001$, uncorrected

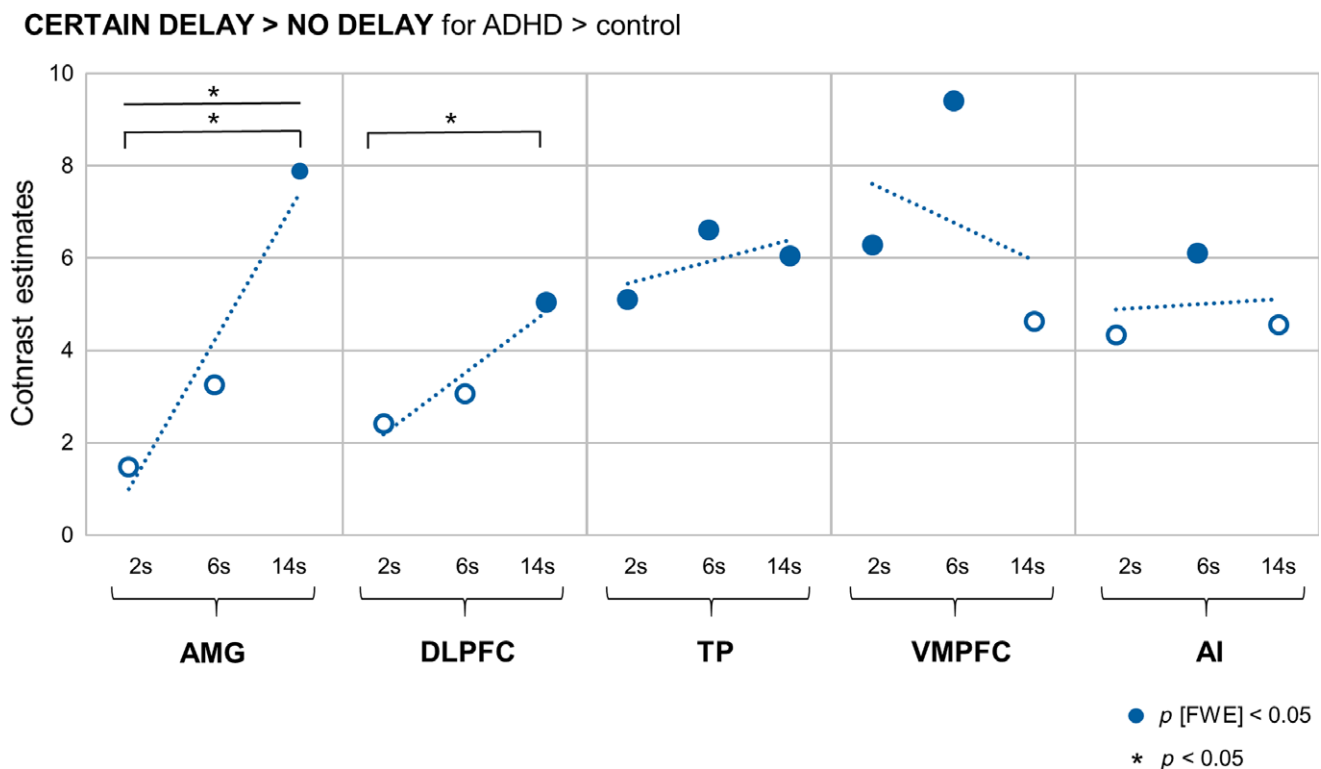


Figure 4 Relationship between delay duration (2, 6, 14 s) and brain activation in amygdala (AMG), dorsolateral prefrontal cortex (DLPFC), temporal pole (TP), ventromedial prefrontal cortex (VMPFC), anterior insula (AI) on the CERTAIN DELAY > NO DELAY contrast in ADHD versus control. A significant ($p < .05$) dose-response effect was shown for the amygdala for ADHD versus control group. Asterisks (*) indicate significant ($p < .05$) post-hoc differences between delay durations. Filled dots indicate significant brain activation ($p < .05$) after family wise error [FWE] correction for a given delay duration [Colour figure can be viewed at wileyonlinelibrary.com]

dependent neural response to cues that consistently predict an impending delay, in both the amygdala and the DLPFC. Second and most importantly, we were able to link this delay-related activation pattern directly to participants' affective experience of delay in everyday life – providing the first evidence that not only do individuals with ADHD show an altered neural response to impending delay, but also their

neural response to impending delay tracks how they subjectively experience delay.

The findings regarding the amygdala were anticipated because of its central role in the processing of delay-related stimuli (Lemiere et al., 2012; Plichta et al., 2009; Wilbertz et al., 2013). Dorsolateral prefrontal cortex hyper-activation to delay cues was not reported in previous studies and was not

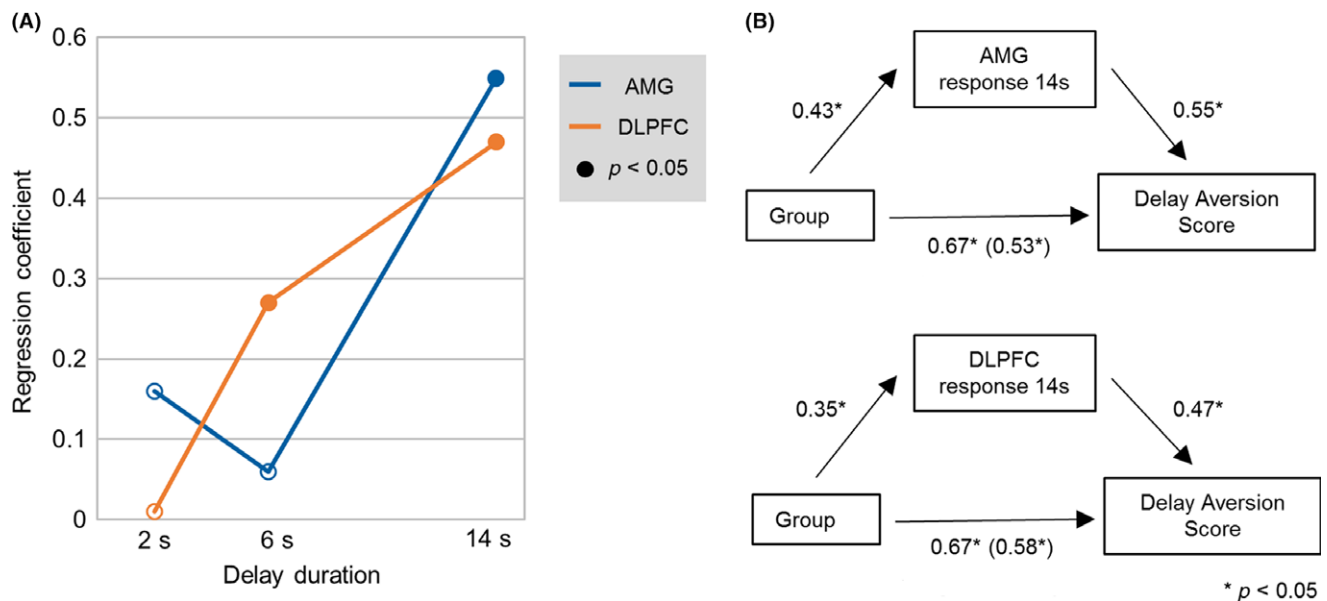


Figure 5 (A) Standardized regression coefficients representing the association between QDQ delay aversion scores and individual peak contrast estimates in amygdala (AMG; blue) and dorsolateral prefrontal cortex (DLPFC; orange) at each delay level. The association increases with longer delays. Filled dots indicate significance at $p < .05$. (B) Models illustrating the way that activation to cues signaling 14-s delay in the AMG and DLPFC mediate the association between ADHD and QDQ delay aversion. The mediated effect for the path between ADHD group and QDQ delay aversion is in parentheses. Asterisks (*) indicate $p < .05$

predicted. However, this region of the prefrontal cortex has shown over-activation to aversive stimuli in a range of other psychiatric disorders such as anxiety (Prater, Hosangagar, Klumpp, Angstadt, & Phan, 2013), depression (Lu et al., 2012), bipolar disorder (Garrett et al., 2012), borderline personality disorder (Dudas et al., 2017) and post-traumatic stress disorder (Aupperle et al., 2012). There are strong interconnections between amygdala and DLPFC, and it is assumed that these two regions combine to promote the avoidance of aversive stimuli, with a central role of the DLPFC in preparatory and control processes prior to the execution of an avoidant response (Bishop, 2008; Gold, Morey, & McCarthy, 2015). Consistent with such a model, the amygdala-prefrontal circuit plays a role not only in emotion regulation (Banks, Eddy, Angstadt, Nathan, & Phan, 2007) but also in effort-based decision making (Floresco & Ghods-Sharifi, 2007). Combining fMRI with electrophysiological measures, allowing more fine-grained temporal distinctions between cue and response related components, can help test this account (Broyd et al., 2012).

In our study, a number of other brain regions, previously implicated in the processing of emotionally charged stimuli, displayed a pattern of enhanced differential activation to CERTAIN versus NO DELAY cues in individuals with ADHD – anterior insula, VMPFC and temporal pole (Hayes & Northoff, 2011; Lindquist et al., 2012). However, these activations did not vary as a function of delay dose. These effects may therefore be driven by the invariance of outcomes predicted by these cues (i.e., circles predict a certain outcome) or their general negative nature

(i.e., circles are generally bad news) rather than their delay-related features. Future experimental studies that manipulate certainty and delay independently can test these possibilities.

Our findings raise questions about the role of the amygdala, and the limbic system more generally, in ADHD pathophysiology. There is growing evidence for smaller amygdala volumes in individuals with ADHD (Plessen et al., 2006), a finding confirmed in a recent large-scale mega-analysis (Hoogman et al., 2017). More generally, structural alterations within the limbic system have been observed in individuals with enhanced impulsivity and emotional lability (Tajima-Pozo, Ruiz-Manrique, Yus, Arrazola, & Montañes-Rada, 2015). Altered amygdala connectivity patterns have also been identified in children and adolescents with ADHD (Bebko et al., 2015; Hulvershorn et al., 2014; Posner et al., 2011). Future studies should directly test the relationship between such alterations in amygdala structure and connectivity on the one hand and amygdala activation in response to delay cues on the other.

From a clinical perspective, the enhanced activation patterns in affective brain networks observed here highlight the importance of considering delay when trying to understand what settings and experiences may elicit negative reactions in individuals with ADHD. These negative responses to delay seem to occur irrespective of possible comorbid patterns of emotional hyper-arousal or dysregulation in ADHD, as only three participants of the ADHD group showed oppositional defiant disorder comorbidity. This has implications for assessment, in that ADHD symptoms and related behaviors may be most

marked in settings incorporating elements of delay (Morsink et al., 2017). In terms of interventions, our findings suggest a need to modify current settings to limit unnecessary delay where possible, while at the same time also motivating a search for ways to increase delay tolerance in individuals with ADHD, perhaps through shaping and fading procedures or the use of desensitization through gradual exposure (Sonuga-Barke, 2004).

This study has many strengths, especially its relatively large sample and the statistical power this provided, the inclusion of three different delay levels that allowed specific effects of delay to be differentiated from other factors, and the use of FWE-correction of the results. There are however also a number of limitations. First, the design of the study included delay-related cues only. It did not, therefore, allow to discern whether the pattern of neural hyper-reactivity was specific to delay aversion or rather an instantiation of a more general hypersensitivity to aversive events. A meta-analysis by Hayes and Northoff (2011) identified a general cross-species aversion-related network that maps onto the same brain regions that were differentially activated by delay cues in this study. This network was shown to be activated independently of sensory modality and did not related explicitly to cognitive processes (Hayes & Northoff, 2011). Studies have found altered amygdala activations in individuals with ADHD symptoms in response to negatively valenced stimuli other than delay, including fearful faces (Posner et al., 2011; Tye et al., 2014), monetary loss (Wilbertz et al., 2015) and threatening cues (Maier et al., 2014). It also remains possible that this network, and the amygdala in particular, processes stimulus salience rather than aversiveness per se (Liberzon, Phan, Decker, & Taylor, 2003). That is, the task used in this study could be picking up a general affective reactivity in ADHD rather than anything specifically to do with responsiveness to aversive events in general or delay in particular. Although we suspect that each of the regions identified in this study is involved in basic aversion-related processing, it is probable that some are also specifically involved in modulating emotion processing. Previous studies have already suggested the involvement of frontal cortical regions in the modulation of amygdala reactivity during successful affect regulation (Gold et al., 2015; Morawetz, Bode, Baudewig, & Heekeren, 2017). Further research should compare amygdala and DLPFC responses to delay cues in individuals with ADHD to responding to cues signalling other aversive (e.g. monetary loss, fearful faces, etc...) and pleasant experiences and events to address these questions.

Second, the task design did not allow us to fully differentiate between brain responses to delay cues and those to cues of certainty/uncertainty outcomes. Some researchers have shown that humans

have a tendency to prefer predictable over unpredictable aversive outcomes, evident behaviorally as well as in terms of reduced activations in aversion-related networks (Labrenz et al., 2016; Sarinopoulos et al., 2009). For adolescents with ADHD, however, fully predictive delay cues elicited significantly higher activations than the less predictive conditional delay cues. It is possible that not having control over outcomes generally, rather than the delay itself, was the aversive aspect of the certain delay trials in the current experiment (Lemiere et al., 2012). However, this cannot explain the finding of a dose-response relationship for the amygdala and DLPFC activations, a finding that readily agrees with the delay aversion hypothesis.

Finally, the sample in this study covers a wide age range (10–18 years). Future longitudinal research should further investigate whether developmental factors play a role in the neurobiological signature of delay aversion (Antrop et al., 2006).

Conclusions

We provide evidence of a direct link between hyper-activation in the amygdala and DLPFC to cues of impending delay and the everyday experience of delay aversion in adolescents with ADHD. Longitudinal studies are required to examine how this association arises and how it is related to the emerging evidence of ADHD-related structural alterations in subcortical brain regions.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. Whole-brain analysis of estimated brain activations in CERTAIN DELAY > NO DELAY anticipation.

Table S2. Whole brain analysis of estimated brain activations in CONDITIONAL DELAY > NO DELAY anticipation.

Figure S1. Scatter plots for the correlations between Quick Delay Questionnaire (QDQ) delay aversion scores and peak brain activations in (A) the amygdala and (B) dorsolateral prefrontal cortex.

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Key points

- Individuals with ADHD rated themselves as more delay averse than controls.
- Cues of upcoming delay elicited an unusually strong pattern of activation within brain regions known to be implicated in the processing of aversive events.
- ADHD-related elevation in activation in response to cues certainly predicting delay relative to cues predicting no delay, in amygdala and dorsolateral prefrontal cortex, was delay-dose sensitive and statistically mediated the relationship between ADHD and self-rated delay aversion.
- Future research should explore whether these neural effects are specific to delay aversion or are a marker of a more general sensitivity to aversive events in individuals with ADHD.
- Clinical practice could benefit from a more detailed understanding of delay aversion as a potential driver of ADHD-related symptoms and comorbidity.

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